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Research Paper

Salicylate-induced hyperacusis in rats: Dose- and frequency-dependent effects

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ABSTRACT

The use of auditory reaction time is a reliable measure of loudness perception in both animals and humans with reaction times (RT) decreasing with increasing stimulus intensity. Since abnormal loudness perception is a common feature of hyperacusis, a potentially debilitating auditory disorder in which moderate-intensity sounds are perceived as uncomfortable or painfully loud, we used RT measures to assess rats for salicylate-induced hyperacusis. A previous study using an operant conditioning RT procedure found that high-dose sodium salicylate (SS) induced hyperacusis-like behavior, i.e., faster than normal RTs to moderate and high level sounds, when rats were tested with broadband noise stimuli. However, it was not clear from that study if salicylate induces hyperacusis-like behavior in a dose- or frequency-dependent manner. Therefore, the goals of the current study were to determine how RT-intensity functions were altered by different doses of salicylate, and, using tone bursts, to determine if salicylate induces hyperacusis-like behavior across the entire frequency spectrum or only at certain frequencies. Similar to previous physiological studies, we began to see faster than normal RTs for sounds 60 dB SPL and greater with salicylate doses of 150 mg/kg and higher; indicating the rats were experiencing hyperacusis at high salicylate doses. In addition, high-dose salicylate significantly reduced RTs across all stimulus frequencies tested which suggests that a central neural excitability mechanism may be a potential driver of salicylate-induced changes in loudness perception and hyperacusis.

1. Introduction

Most people find that sounds around 100 dB HL are uncomfortably loud (Sherlock and Formby, 2005) while sound intensities above 140 dB SPL evoke the sensation of pain and discomfort (Ades et al., 1959). However, about 6% of adults suffer from hyperacusis, a debilitating condition in which sounds of moderate intensity are perceived as intolerably loud or even painful, leading to negative emotions, a dependence on hearing protective devices, and avoidance of social situations (Anari et al., 1999; Katzenell and Segal, 2001; Andersson et al., 2002; Tyler et al., 2014; Chen et al., 2015). Among patients with a primary complaint of hyperacusis, more than 80% also suffer from tinnitus (Anari et al., 1999; Andersson et al., 2002; Dauman and Bouscau-Faure, 2005; Tyler et al., 2014) whereas among those with a primary complaint of tinnitus, about 40% also experience hyperacusis (Baguley, 2003). However, the prevalence of hyperacusis is likely much higher since most tinnitus patients are unaware of their loudness intolerance condition unless explicitly tested (Gu et al., 2010).

Given the frequent co-occurrence of tinnitus and hyperacusis, it is conceivable that these auditory disorders arise from a common mechanism within the auditory pathway (Gu et al., 2010; Hébert et al., 2013; Chen et al., 2015). Experimentally, sodium salicylate (SS), the active ingredient in aspirin, has long been known to induce temporary hearing loss and acute tinnitus in both humans and animals and it has served as an extremely useful model to investigate the neural and biological mechanisms underlying tinnitus and hearing loss (Myers and Bernstein, 1965; Mongan et al., 1973; McFadden et al., 1984; Brennan et al., 1996; Cazals, 2000; Stolzberg et al., 2012b; Sheppard et al., 2014; Chen et al., 2015). While high doses of salicylate are known to induce tinnitus in animal models, more recent studies indicate that salicylate also enhances the amplitude of the acoustic startle reflex, results interpreted as evidence of hyperacusis but may also be related to

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stress (Ison et al., 2007; Sun et al., 2009; Chen et al., 2014). There are, however, a number of limitations to using the acoustic startle reflex to assess loudness growth and hyperacusis. The reflex can only be elicited at relatively high sound levels (>80 dB SPL) and has a limited dynamic range since the startle response saturates at approximately 115 dB SPL (Lobarinas et al., 2013), however lower sound levels may be used to assess hyperacusis with prepulse inhibition (Turner and Parrish, 2008; Hickox and Liberman, 2014).

Previous studies in both humans and animals have established that reaction time (RT), the time between the onset of a stimulus and the response by a listener, is highly correlated with loudness perception across a wide range of stimulus levels and frequencies (Arieh and Marks, 2003; Wagner et al., 2004) for both normal-hearing (Marshall and Brandt, 1980; Leibold and Werner, 2002) and hearing-impaired listeners (Pfingst et al., 1975). In both humans and animals, there is an inverse relationship between RT and stimulus intensity, i.e., RT decreases with increasing stimulus intensity (Stebbins and Miller, 1964; Stebbins, 1966; Moody, 1973; Marshall and Brandt, 1980; Leibold and Werner, 2002; Lauer and Dooling, 2007; May et al., 2009). In a standard reaction time experiment, a listener responds to a sound, typically a pure tone, and the time it takes the listener to make a given response is recorded by the researcher. For adult humans, the response is typically a hand raise or button press (Marshall and Brandt, 1980; Arieh and Marks, 2003; Wagner et al., 2004). Researchers have also used a head turn as the response to measure auditory reaction time in infants (Leibold and Werner, 2002). Similar to humans, auditory reaction time is assessed in animals by measuring the time it takes an animal to make a response, i.e., a lever press (Stebbins and Miller, 1964; May et al., 2009), key peck (Lauer and Dooling, 2007), or nose poke (Chen et al., 2014), in response to a sound stimulus. The biggest procedural difference between human and animal reaction time studies is that humans can be instructed how to perform the task whereas animals have to be trained to perform the task.

In animals with noise-induced hearing loss, RT-intensity functions showed evidence of loudness recruitment in regions of hearing loss, i.e., at low stimulus intensities, RTs were slower than normal, but as intensity increased RT rapidly decreased and became equal to pre-exposure RT values (Moody, 1973; May et al., 2009). While RT studies have found evidence of loudness recruitment in hearing-impaired mammals, one study reported that canaries with high-frequency hereditary hearing loss had faster than normal RTs at high sound intensities. These results suggest that certain types of hearing loss might induce hyperacusis (Lauer and Dooling, 2007).

Since salicylate causes cochlear hearing loss, induces tinnitus, and enhances sound-evoked neural activity in the central auditory pathway, we measured RT-intensity functions to noise bursts before and after treating rats with a high dose of salicylate (Chen et al., 2014). In these preliminary studies, RTs were slower than normal at low intensities due to the salicylate-induced hearing loss, but as intensity increased there was a striking reduction of RT at moderate-to-high intensities (Chen et al., 2014, 2015). These results suggested that the rats were not only experiencing tinnitus, but also hyperacusis at sound levels above 50 dB SPL. Since salicylate is known to induce tinnitus at high doses ($\geq$150 mg/kg) (Lobarinas et al., 2004), the goal of the current study was to extend our earlier findings to: (1) Using noise bursts, determine how RT-intensity functions were altered by different doses of salicylate (i.e., which doses of salicylate induced hyperacusis and over what intensity range does hyperacusis occur?), and (2) Using tone bursts, determine if salicylate induces hyperacusis-like behavior across the entire frequency spectrum or only at certain frequencies (i.e., hyperacusis spectral profile).

2. Materials and methods

2.1. Subjects

Seven Sprague-Dawley rats (2 male, 5 female) were obtained from Charles River Laboratories and were used in the operant conditioning task. All rats were individually housed and kept on a 12 h day/night cycle, lights on at 6 a.m. and off at 6 p.m. The rats started training at approximately 3–4 months of age. The rats were food restricted during the course of the experiment but were kept at or above 85% of their free-feeding weight. Rats had unrestricted access to water, except during testing. The test sessions ran for approximately 1 h a day, 6–7 days a week. All the procedures were approved by the University at Buffalo, SUNY's Institutional Animal Care and Use Committee.

2.2. Apparatus

Rats were tested in an acoustically transparent acrylic cage (28 × 30 × 38 cm) located inside a sound attenuating chamber (76 × 71 × 71 cm) lined with 5 cm thick sound attenuating foam (Illbruck, Inc., Minneapolis, MN, USA). The behavior of the animals during test sessions was monitored by a digital camera (Fire-i Digital Camera, Unibrain, San Ramon, CA, USA). The test cage was equipped with a speaker (FT28D Dome Tweeter, Fostex, Tokyo, Japan), feeder (Med Associates Model ENV-203M, St. Albans, VT, USA), and nose-poke hole equipped with infrared sensors (Vulintus, Dallas, TX, USA).

The experiment was conducted using custom behavioral software running on a personal computer (Microsoft Windows XP) described in a previous experiment (Stolzberg et al., 2013). The custom software controlled Tucker-Davis Technologies (TDT, Gainesville, FL) system-3 equipment. Sound stimuli were generated with TDT hardware and software (TDT RX6 processor, D/A converter, ~100 kHz sampling rate); digital inputs to and outputs from the testing cages were controlled by the TDT RX6 processor interfaced to a pellet feeder (Med Associates Model SG-501, St. Albans, VT, USA) and infrared sensors (Vulintus, Dallas, TX, USA). TDT RPvds software and custom MATLAB software (MathWorks, Nattick, MA, USA) were used to control all aspects of the experiment (Radziwon et al., 2015). Sound pressure levels were calibrated using a sound level meter (Larson Davis System 824; Fast setting; Flat weighting applied) equipped with a microphone (1/2″ free field microphone, model 2520, Larson-Davis, Depew, NY, USA) placed at the position where the animal's head would be when its nose is inside the nose poke hole.

2.3. Stimuli

The stimuli used in the reaction time experiments were broadband (BBN) noise bursts (1–42 kHz bandwidth, 300 ms duration, 5 ms cosine rise/fall times) and tone bursts (4, 8, 16, and 20 kHz, 300 ms duration, 5 ms cosine rise/fall times). The stimuli were presented at 30, 40, 50, 60, 70, 80, and 90 dB SPL. The rats were trained to detect the noise bursts and tone bursts in a quiet background using a go/no-go operant conditioning procedure.

2.4. Procedure

The first phase of the training process consisted of shaping the rat to poke its nose into the nose-poke hole and then going to the feeder trough for a food reward. Once the rats were reliably nose-poking, the auditory stimuli were introduced. As the rats continued their training, the waiting interval was systematically increased from 1 to 4 s, and catch trials were added.